

### **REMARKS**

Reconsideration is respectfully requested in view of the foregoing amendments and the following remarks. Claims 26, 28, 29 and 40 have been amended. Support for the amendments is to be found in the as-filed specification.

Claims 26-45, inclusive, are pending herein.

The objection to the specification has been remedied by providing pages 3, 4 and 5, which are intact. The missing structure at the bottom of each of the pages was caused by a printing error. The pages were filed in a complete fashion. No new matter has been added.

The § 112, second paragraph, rejection for indefiniteness is traversed.

As regards the definition of D(0.5) etc., in the originally filed specification it is clearly pointed out that they pertain to the granulometric distribution is as disclosed in the specification. In fact, it is universally accepted that D[4.3] is the value of the average diameter measured as a function of the volume distribution (average of all the observations). While D(0.5) is the medium value, it represents the diameter, dividing the distribution exactly in half (50% of the distribution is above and 50% is below that value). When the distribution is a gaussian (ideal), the two values coincide.

In claims 29, 37 and 40, “preferably” and “possibly” have been cancelled.

In claim 28 --or -- has been substituted for “of”.

In claim 26, Formula VI has been corrected.

In view of the foregoing, the § 112 rejection has been overcome and should be withdrawn.

Claims 26-45 stand rejected under 35 U.S.C. § 103(a) over Jones et al. (U.S. 4,358,593 (Jones 1) in view of Jones et al. (EP 62503) (Jones 2) and in further view of Alt (U.S. 5,523,416). This rejection is traversed.

Before addressing the Examiner's rejection under § 103(a), it might be helpful to point out the gist of the instant invention.

As was clearly pointed out in EP62503 (Jones 2) (the originally filed Jones reference cited by the Examiner) it disclosed: raloxifene, for the first time and various preparative methods involving the following stages:

- 1.) protection of the two hydroxilic groups of 6 -hydroxy -2-(4-hydroxyphenyl)-benzol[b]thiophene with alkyl, acyl or sulphonyl groups;
- 2.) acylation of the compound protected with 4-(2-piperidinoethoxy)-benzoyl halide; and,
- 3.) deprotection or elimination of the protective group.

From the results of the examples reported in EP62503 (Jones 2), when the reaction is carried out using the acetyloxy group as a protecting group, deprotection of these groups is carried out first with sodium hydroxide in an alcoholic solution, and subsequently with methane sulphonic acid. However, this type of hydrolysis does not allow for the obtention of high purity raloxifene since, as indicated by example 6 of said reference, the product after being rendered basic with ammonia in order to isolate it, must be passed through a chromatographic column. This type of treatment only enables a yellow foam to be obtained. To arrive at a product in crystalline form, a further treatment with acetone is required. The crystalline product thus obtained consisting of raloxifene, must then be converted to the corresponding hydrochloride salt.

The aforesaid process requires passage through a chromatographic column and cannot be achieved on an industrial scale. Proof of the foregoing is provided in the same patent, where it is disclosed that instead of the aforesaid scheme, the preferred scheme is

one in which the protective group is an alkoxy group, specifically a methoxy, which for unblocking requires the use of aluminium trichloride and a thiodervative, such as methanthiol. Moreover, it must be used in a quantity which is greatly in excess with respect to the substrate, which engenders considerable pollution problems. This deprotection moreover causes another problem as a result of the need to use aluminium trichloride which must be used in considerable quantities and, moreover, not only in the acylation step but also in the deprotection step.

In order to overcome this aspect, the successor patent U.S. 5,629,425 proposes a process involving protection with the alkoxy group with the use of boron trichloride, which is very expensive.

The need was felt to have a process enabling the preparation of raloxifene hydrochloride with high purity and in high yields with a low aluminium content without using expensive catalysts.

Applicants herein have discovered such a process enabling the preparation of raloxifene hydrochloride in high yields and with a high degree of purity when it is still in the crude form.

This process comprises the following steps:

- a.) demethylation of 6-methoxy -2-(4 methoxyphenyl) benzo[b]thiophene in the presence of pyridine hydrochloride to obtain 6-hydroxy-2-(4-hydroxyphenyl)-benzo[b]thiophene;
- b.) acetylation of the intermediate obtained in step (a) with an acetylating agent to obtain the corresponding 6-acetoxy -2-(4-acetoxyphenyl) benzo[b]thiophene;
- c.) acylation of the intermediate obtained in the previous step with 4-(2-piperidinoethoxy) benzoylchloride hydrochloride with aluminium chloride in halogenated solvent to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene;

- d.) hydrolysis of the intermediate according to the following operative modalities:
  - d1) treatment of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl benzo[b]thiophene with sodium hydroxide in the presence of an excess of 30% sodium hydroxide,
  - d2) acidification of the reaction mixture obtained in d1 with equal weight of water and ethyl acetate and 37% HCl, washing the suspension filtered by centrifugation and the solid obtained after being washed with equal amount of water and ethyl acetate and is finally dried.

In fact, the HPLC purity of the crude product is **98%** with yields in the range of **65-70%** calculated on the 6-methoxy -2-(4 methoxyphenyl) benzo[b]thiophene (see page 5, lines 9-12 and page 7, lines 7-9 of the specification).

An analysis of Jones U.S. 4,358,593 (Jones 1), the primary reference employed by the Examiner reveals that it is not very different from EP62503 (Jones 2).

In fact, Jones 1, like Jones 2, also encompasses a process for preparing, among other compounds, raloxifene, involving the following steps:

- 1.) protection of the two hydroxilic groups of 6 -hydroxy -2-(4-hydroxyphenyl)-benzo[b]thiophene with alkyl, acyl or sulphonyl groups;
- 2.) acylation of the compound protected with 4-(2-piperidinoethoxy) – benzoyl halide; and,
- 3.) deprotection or elimination of the protective group.

Also, in this case the deprotection of the acetyl group is carried out using the same procedure disclosed in Jones 2 (see example 26 of Jones 1). In other words, Jones 1, by hydrolysing at an alkaline pH and adding methane sulphonic acid to the mixture and subsequently rendering it basic with ammonia and finally purifying by passing it through a chromatographic column, follows a similar procedure to Jones 2.

In addition, the passage underlined by the Examiner at column 8, lines 8-30 must be read carefully, since, although it is said that the salts are quickly formed in high yields by reacting the compound in a suitable organic solvent and are obtained by merely isolating the compound in an acidic wash, as it results from Jones 1 and also Jones 2, **this is not the case** for the salt obtained with methane sulphonic acid. In addition, the same Jones 1 in the aforementioned passage for preparing the hydrochloric acid, even suggests dissolving the **isolated** free base, such as raloxifene, in an organic solvent and to bubbling in hydrogen chloride.

In view of the foregoing, Jones 1 discloses operative conditions **decidedly far removed from those of the process claimed**, wherein **the reaction mixture**, and not the isolated product resulting from the alkaline hydrolysis with sodium hydroxide, is **directly** treated with concentrated **aqueous** hydrogen chloride, and not with gaseous hydrogen chloride bubbled in an organic solvent as in Jones 1.

It follows from the foregoing that Jones 1 is addressing a salification of the **already isolated free base** (raloxifene), moreover Jones' use of **strictly anhydrous conditions** would have led one of ordinary skill in the art *away* from even conceiving of the claimed process, wherein aqueous concentrated hydrochloric acid is added **directly** to the reaction mixture issuing from the alkaline hydrolysis, thus enabling the obtention of raloxifene hydrochloride having a high purity, even in crude form and, moreover, in high yields.

The teachings of Jones 2 could in no way enable the skilled person to overcome the deficiencies in Jones 1 teachings since, as pointed out above, its teachings are in the same direction as Jones 1, taking into account that the sole direct salification of a reaction mixture disclosed in Example 6 is the aforementioned reaction with methane sulphonic acid where only a yellow foam is obtained.

In view of the foregoing, Applicants respectfully traverse the Examiner's § 103(a) rejection that it would be obvious to initiate the synthesis of the desired final products raloxifene hydrochloride by Jones 1 procedure by changing the starting material (6-methoxy-2-(4 methoxyphenyl) benzo[b]thiophene as taught in Jones 2, also considering

the teaching of Alt U.S. 5,523,416 that (6-methoxy-2-(4methoxyphenyl) benzo[b]thiophene can be deprotected with pyridine hydrochloric acid. A further argument beyond the above arguments, is that Jones 2, at most, suggests a synthetic scheme in which the alkoxy group is **only** used as a protecting group in the acylation reaction and **not** as the starting reactant, as in the instantly claimed process, wherein the effective protecting group in the acylation reaction is the acetoxy group.

For the above reasons, applicants respectfully submit that the combination of prior art as proposed by the Examiner besides being misleading, must be also considered as being untenable. Thus, applicants respectfully submit that the claims distinguish over the combination of references applied by the Examiner, since a *prima facie* case of obviousness has not been established, Withdrawal of the § 103(a) rejection is solicited.

As regards Alt, U.S. 5,512,684 a reference considered pertinent to Applicants' disclosure by the Examiner, it comprises the following steps, see col. 2, line 19:

- a.) optionally dealkylating 6-alkoxy -2-(4 methoxyphenyl) benzo[b]thiophene in the presence of pyridine hydrochloride to obtain 6 -hydroxy -2-(4-hydroxyphenyl)-benzo[b]thiophene, of formula (II);
- b.) acylating the intermediate obtained in step (a) with an acylating agent to obtain the corresponding 6-acyloxy -2-(4-acyloxyphenyl) benzo[b]thiophene of formula (II);
- c.) acylation of the intermediate obtained in the previous step with an N(R1R2)-benzoylchloride hydrochloride wherein R1 and R2 may form a C<sub>4</sub>-C<sub>6</sub> polymethylene group with aluminium chloride in halogenated solvent to obtain 6-acyloxy-2(4-acetoxyphenyl)-3-[4-(2-benzoyloxyCH<sub>2</sub>CH<sub>2</sub>-NR<sub>1</sub>R<sub>2</sub>)]benzo[b]thiophene; and
- d.) cleaving the protecting acyl group.

From the examples reported in Alt '684, the skilled person could in no way foresee the process according to the claimed invention, which encompasses, as the final steps, hydrolysis in alcoholic solvents in the presence of sodium hydroxide, and the direct precipitation of raloxifene hydrochloride as a solid with a HPLC degree of purity greater than 98% by the addition of 37% HCl to the reaction mixture resulting from the alkaline hydrolysis, and without isolating the free base raloxifene.

In fact, in example 6, of Alt '684, there is disclosed the preparation of a different compound from raloxifene by hydrolysis with sodium hydroxide in methanol followed by a series of acidification and basification steps which inevitably would lead the skilled person away from the claimed process, and moreover, prevent a skilled artisan from even conceiving of the presently claimed process.

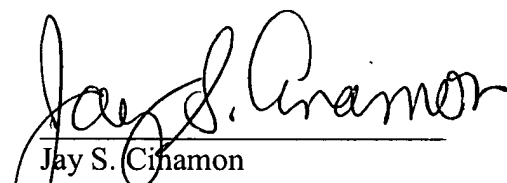
Since the objection and the rejections have been overcome, the issuance of a Notice of Allowance is solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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The processes described in EP62503 involve another inconvenience caused by the use of aluminium trichloride and, if proceeding to the scheme preferred by this prior patent, this Lewis acid must be used in substantial quantities, since it is used not only in stage (2) of acylation, but also in subsequent dealkylation. Aluminium trichloride as shown in the subsequent patent US5629425 produces a large quantity of aluminium-based by-products which are soluble in raloxifene processing solvents and are found therefore in the final product.

To overcome these problems, in the aforesaid US5629425 boron trichloride or boron tribromide is used as Lewis acid, these being decidedly more expensive catalysts than aluminium trichloride.

The need was felt to provide a process which enabled raloxifene hydrochloride to be prepared with high yields and high purity and low aluminium content without using expensive catalysts.

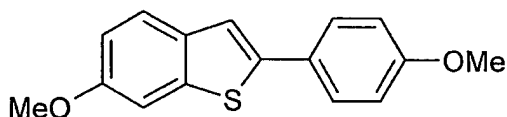
#### Summary of the invention

The applicant has surprisingly found a process capable of overcoming the drawbacks of known processes and which allows raloxifene and in particular raloxifene hydrochloride to be obtained with high purity and high yields.

This process comprises in particular the following stages:

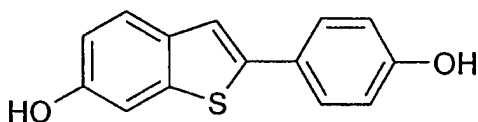
a) demethylation of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene of formula

(II)



(II)

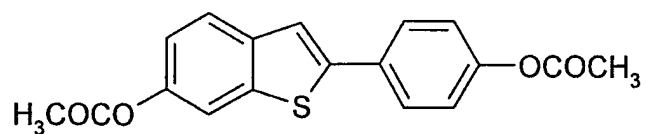
in pyridine hydrochloride to obtain 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene of formula (III)



(III)

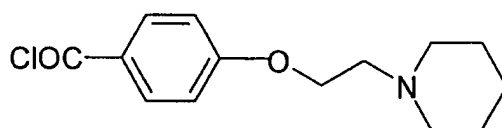
b) acetylation of 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene with an acetylating agent to obtain the corresponding 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene of formula (IV)

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(IV)

10 c) acylation of 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride of formula (V)



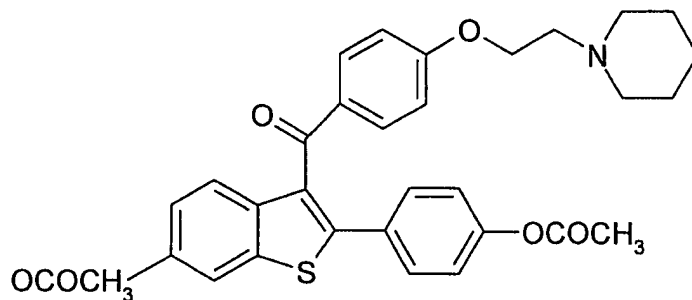
HCl

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(V)

with aluminium trichloride in halogenated solvent to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene of formula

20 (VI)



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(VI)

d) hydrolysis of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene, according to the following operative methods:

d1) treatment of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene with alkaline hydroxide in alcohol solvent,

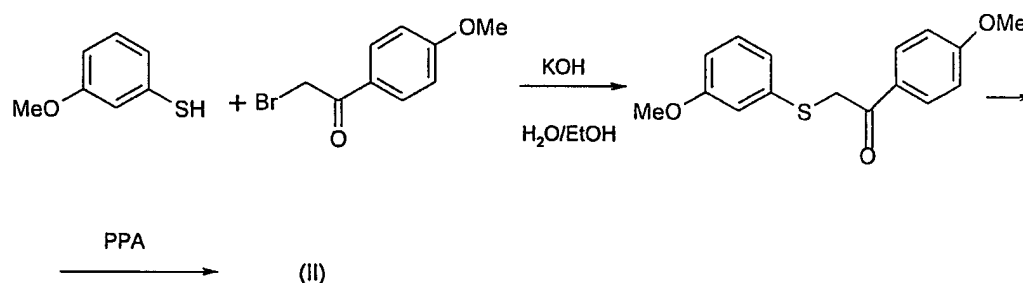
5 d2) acidification of the product obtained in the previous stage (d1) with a strong acid, to obtain the corresponding raloxifene salt with strong acid, characterised in that the strong acid used in stage (d2) is concentrated hydrochloric acid.

In this respect, by conducting the hydrolysis of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene with sodium hydroxide and subsequently treating the product obtained with hydrochloric acid in place of methanesulfonic acid, raloxifene hydrochloride precipitates in crystalline form directly with a high purity equal to 98%, thus in contrast to the analogous process described in EP65203 conducted with methanesulfonic acid, without having to use purification processes such as passage through a chromatographic column, which are impractical from the industrial point of view. In addition the product derived from stage (d2) has a low aluminium content.

#### Detailed description of the invention

The 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene of formula (II) used in stage (a) of the process of the present invention is prepared by reacting 3-methoxybenzene-thiol with  $\alpha$ -bromo-4-methoxyacetophenone to obtain the corresponding  $\alpha$ -(3-methoxyphenylthio)-4-methoxyacetophenone which is finally cyclized to obtain the intermediate (II) with polyphosphoric acid, as in the following scheme.

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